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RENAL FUNCTION AND THE EXCRETION OF POTASSIUM IN ACUTE ALKALOSIS

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Gross potassium deficiency has been demonstrated in states of metabolic alkalosis in man (Mudge & Vislocky, 1949) and in the experimental animal (Darrow, 1946; Darrow, Schwartz, Ianucci & Coville, 1948). The cause of this potassium deficiency is not clearly established, because alkalosis is usually complicated by other severe metabolic disorders, such as dehydration and starvation, which are known to be associated with impaired renal function (McCance & Widdowson, 1937; Burnett, Burrows, Commons & Towery, 1950) and an increased loss of potassium in the urine. For this reason a study of potassium excretion and of renal function has been made in experimental alkalosis uncomplicated, as far as is possible, by other factors known to affect the excretion of this ion. The acute alkalosis was produced in dogs or in man by three different methods; the removal of chloride ions by peritoneal dialysis with bicarbonate solutions; the intravenous infusion of sodium bicarbonate; and by prolonged overbreathing.

METHODS

Dog experiments

Six experiments were completed on three young female dogs (wt. 8–11 kg) under pentobarbitone sodium anaesthesia. The dogs were fasted for 18 hr before the experiments, and did not receive additional supplements of potassium at any time. Before the development of alkalosis there was a 2 hr period of equilibration in which a slow intravenous drip was given containing inulin, sodium *p*-aminohippurate (PAH) and 5% (w/v) glucose, at 3 ml./min.

Chloride depletion alkalosis. After the equilibration period chloride ion was removed by intermittent dialysis of the peritoneum with the following solution: Na, 140 m.equiv/l.; HCO_3, 140 m.equiv/l.; K, 4 m.equiv/l.; Cl, 4 m.equiv/l.; glucose, 30 g/l.; inulin, 20 mg; PAH, 4 mg/100 ml. A metal cannula was inserted into the peritoneal cavity and 500 ml. of warm dialysis solution was run in, and then syphoned out again after 15–20 min. This cycle of operations was repeated continuously over the next 2 hr, using a total of 3–4 l. of dialysis fluid in each experiment. The intra-abdominal pressure was measured by a water manometer, and, by altering the level of the

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fluid reservoir, it was adjusted to oscillate around +2 cm of water. Blood and urine samples were taken every 30 min and measurements made of the pH, electrolyte composition and concentration of inulin and PAH. There were three experiments of this type, providing sixteen clearance periods during alkalosis produced by chloride deficit.

Bicarbonate alkalosis. Following the equilibration period, 5% (w/v) sodium bicarbonate was infused intravenously at 3 ml./min for 120 min. Blood and urine samples were taken and analysed as in the previous experiments. Three experiments were completed, providing eighteen clearance periods during bicarbonate alkalosis of increasing severity.

Blood collection. Blood was taken from the uncompressed external jugular vein into oiled, heparinized 20 ml. syringes. The pH was measured immediately as described below. The remainder of the specimen was centrifuged under paraffin, and the CO_2 content of the plasma was measured within 5 min of taking the blood.

Urine collection. Urine was collected with special precautions to prevent the loss of CO_2. A rubber catheter was placed in the bladder and all specimens were taken under paraffin. At the end of each clearance period the bladder was emptied by manual compression over the lower abdomen. In order to avoid errors in the determination of urine pH and CO_2 content the bladder was not washed out. The high rates of urine flow, 1–3 ml./min, and long clearance periods made accurate collection possible. Samples of urine were taken by pipette for measurement of CO_2 content and pH. These were made at once and without contact with the air.

Renal clearance techniques. The clearance of inulin (C_{IN}) and of PAH (C_{PAH}) were determined by the methods of Smith, Finkelstein, Aliminosa, Crawford & Graber (1945) and Shannon (1935). A constant infusion was obtained by an automatic syphon burette (Sellick, 1951) combined with a tunnel clamp (Bradley, 1947). The inulin clearance was taken as a measure of the filtration rate, and that of PAH as the renal plasma flow. The symbols C_K, C_{Na}, C_{HCO_3} have been used for the clearance of potassium, sodium and bicarbonate.

Measurement of the inulin space. The inulin space has been used as a measure of the extracellular fluid volume (Gaudino & Levitt, 1949), using the difference technique (Crawford & Gaudino, 1952). Besides the collection and accurate timing of all the urine specimens, the method requires the slow infusion of inulin over a period of 2 hr for the initial equilibration, and the measurement of the total quantity of inulin infused by an accurate burette. The amount of inulin retained at any time was then calculated as the difference between the total infused and the cumulative excretion. The inulin space was obtained by dividing the figure for the retained inulin by the concentration of inulin in the plasma at that time.

Human experiments

Acute respiratory alkalosis. Observations were made on three normal males, commencing 2 hr after meals. Sufficient water was taken to ensure a urinary output of 2–4 ml./min. Each of the six experiments comprised 6–8 periods of 15 min, and at the end of each period the urine volume, pH and electrolyte content were measured. In the third and fourth periods the subjects overbreathed deeply and regularly, producing a severe respiratory alkalosis. The inulin clearance, blood pH, plasma CO_2 and electrolyte content were also measured in four similar experiments, providing twenty-eight clearance periods, including eight in respiratory alkalosis. The clearance techniques used were those described by Goldring & Chasis (1944), except that the subjects were not catheterized. They were trained to empty the bladder, which was done while standing. In five of the ten experiments 60 m.mole KCl was taken by mouth 1 hr before the period of hyperventilation.

Methods of analysis

pH determination. Samples of urine and whole blood, collected as described, were transferred without contact with air to the glass electrode chamber of a Stadie apparatus. The water-bath was kept at 37° C by an electric heater. A Cambridge pH meter was used for the determinations, and was calibrated by standard buffer solutions between each estimation.

Chemical. CO_2 content, Van Slyke & Neill (1924); sodium and potassium, internal standard flame photometry (Spencer, 1950); chloride, Whitehorn (1921), and mercurimetric (Schales &

Schales, 1941); magnesium (Briggs, 1922; Kunkel, Pearson & Schweigert, 1947); phosphorus (Fiske & Subbarow, 1925); ammonia (Hawk, Oser & Summerson, 1947); inulin and PAH (Goldring & Chasis, 1944).

RESULTS

Dog experiments

Potassium excretion. The effects of acute metabolic alkalosis on potassium excretion in dogs were similar in the six experiments, whether produced by chloride depletion or by the intravenous infusion of bicarbonate (Figs. 1 and 2, Table 1). As the alkalosis developed the renal excretion of potassium increased

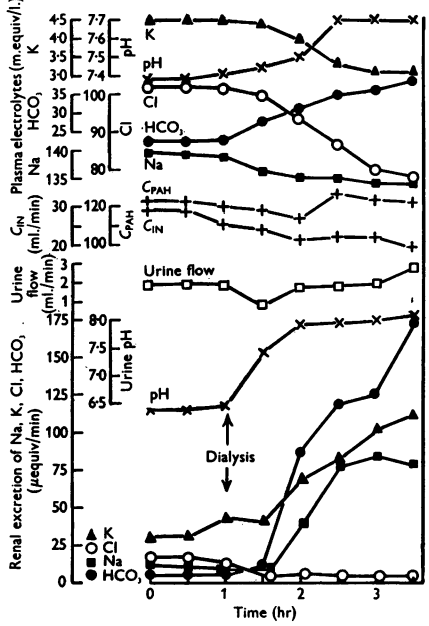

Fig. 1.

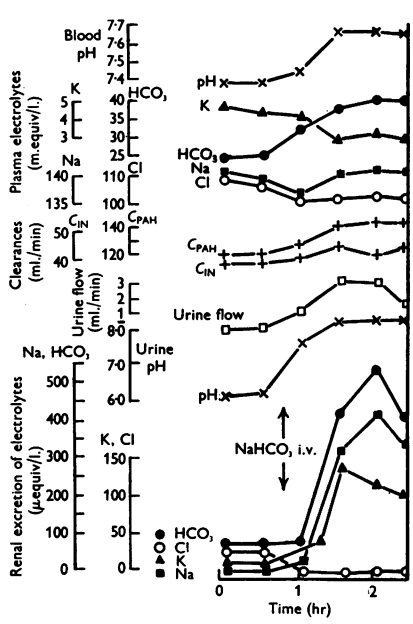

Fig. 2.

Fig. 1. The effect of acute chloride depletion alkalosis on renal function (dog 3). Chloride removed by differential peritoneal dialysis starting at ↕ and continuing for 2 hr.

Fig. 2. The effect of sodium bicarbonate infusion alkalosis on renal function (dog B1). 5% $NaHCO_3$ was infused at 3 ml./min beginning at ↕ and continuing for 2 hr.

three to four times. The plasma potassium usually decreased from 4·5 to 2–3 m.equiv/l. and the load of potassium filtered at the glomerulus fell progressively. This was more evident in the chloride depletion experiments, in which there was also a fall in the filtration rate. Paradoxically, during alkalosis the rate of potassium excretion increased despite the fall in the filtered load of potassium. The clearance ratio C_K/C_{IN} rose from 0·15 at a blood pH of 7·3 to a maximum of 2·0 at a blood pH of 7·75 (Table 1). Potassium excretion

increased, although there was a negative balance for this ion resulting from continued losses in the urine.

Sodium excretion. During the infusion of sodium bicarbonate the dogs reached a positive sodium balance of 15–20 m.equiv/kg (Table 2). The rate of sodium excretion increased from 10 to 448 μequiv/min (Fig. 2, Table 1), and the clearance ratio C_{Na}/C_{IN} rose from 0·001 to 0·09. In the chloride depletion experiments there was a small increase in sodium excretion up to 79 μequiv/min, although the filtered load of sodium was decreased.

TABLE 1. Acute metabolic alkalosis in the dog, produced by intravenous sodium bicarbonate, or by chloride depletion during peritoneal dialysis. The blood pH and data relating to the excretion of potassium and other electrolytes

Expt.	Blood pH	Plasma concn. (m.equiv/l.) Na	K	HCO_3	Cl	C_{IN} (ml./min)	C_K/C_{IN}	K load (μequiv/min) $C_{IN} \times K_P$	Excretion rates (μequiv/min) K	Na	HCO_3	Cl
Intravenous $NaHCO_3$												
Dog 1, 9 kg	7·35	138	4·2	24	103	38	0·05	160	8	2	1	5
	7·65	140	2·9	38	97	45	1·08	131	141	310	408	0
Dog 1B, 9 kg	7·40	143	4·0	25	102	37	0·3	148	45	85	5	10
	7·70	145	4·0	39	94	36	1·29	144	186	448	420	0
Dog 2, 8 kg	7·35	140	4·4	25	97	32	0·1	152	15	16	0	2
	7·60	139	2·8	37	84	31	0·6	87	51	393	380	0
Cl removal												
Dog 2, 8 kg	7·34	141	4·2	25	102	30	0·1	126	16	14	1	10
	7·70	135	2·2	37	70	19	2·0	42	84	41	136	0
Dog 3, 11 kg	7·40	140	4·6	23	102	39	0·21	178	38	12	0	6
	7·75	134	3·1	37	76	19	1·9	57	112	79	167	0
Dog 1, 9 kg	7·20	140	4·5	22	104	32	0·1	144	14	16	0	12
	7·50	130	4·1	35	80	18	0·8	74	61	39	142	0

Bicarbonate excretion. The plasma bicarbonate rose to 35–40 m.equiv/l. in both types of alkalosis, and the renal excretion increased up to 500 μequiv/min (Figs. 1 and 2, Table 1). The increment in bicarbonate excretion was equal to the rise in the filtered load, and the ratio C_{HCO_3}/C_{IN} consistently rose from normal values of less than 0·001 to 0·30 during severe alkalosis.

Chloride excretion. During the peritoneal dialysis experiments the chloride ion removed was approximately 9 m.equiv/kg (Table 2), and the plasma chloride fell to 70–80 m.equiv/l. (Fig. 1, Table 1). Chloride disappeared from the urine at an early stage of each experiment and before there was any considerable change in the filtered load of this ion. In the alkalosis of bicarbonate infusion there was a small (6–12 m.equiv/l.) fall in the plasma chloride. As there was usually a coincident slight rise (5–10%) in the filtration rate the filtered load of chloride was not appreciably reduced. Nevertheless, chloride again disappeared from the urine.

Other ions. In both types of alkalosis the excretion of ammonia decreased, and ceased at a urine pH 6·8–7·2. Phosphate excretion increased two- to fourfold, allowing for the increased equivalence of this ion at the higher pH of the urine.

Renal blood flow and filtration rate. The C_{IN} and C_{PAH} were maintained at normal levels or increased slightly (5–10%) in the sodium bicarbonate infusion experiments (Fig. 2, Table 1). During peritoneal dialysis, however, they were both low, and decreased further as the experiments progressed (Fig. 1, Table 1). The rates of urine flow were also lower in these experiments (Table 2). This disturbance in renal function began early in the experiments, and appeared to result from the technique of dialysis rather than from the alkalosis.

TABLE 2. Acute metabolic alkalosis in the dog, produced by intravenous sodium bicarbonate or by chloride depletion during peritoneal dialysis. The external balances of water and electrolytes, the inulin spaces, and the apparent changes in cell water

Expt.	Urine vol. (ml./min)	External balances				Inulin space (ml.)	Cell water change (ml.)
		H_2O (ml.)	Na (m.equiv)	K (m.equiv)	Cl (m.equiv)		
Intravenous $NaHCO_3$							
Dog 1, 9 kg	2·2	+611	+205	−12	−2	1240 before 1830 after +590	+ 21
Dog 1B, 9 kg	1·3	+248	+174	−8	−3	1450 before 1430 after −20	+268
Dog 2, 8 kg	2·2	+287	+147	−26	−2	1620 before 1870 after +250	+ 37
Cl removal							
Dog 1, 9 kg	0·9	+279	+50	−13	−83	1700 before 1430 after −270	+549
Dog 2, 8 kg	1·4	+358	−16	−8	−91	1820 before 1940 after +120	+238
Dog 3, 11 kg	1·7	+453	+9	−18	−90	1800 before 2080 after +280	+173

Changes in body water. The total external balances of water gradually increased during the experiments and reached a maximum of +3–6% of the body weight. The apparent changes in the distribution of body water were calculated from the cumulative water balance and the inulin space (Table 2). In each experiment there was a moderate increase in cell water.

Hyperventilation alkalosis in man

Hyperventilation alkalosis was regularly associated with a two- to fourfold increase in the excretion of potassium (Fig. 3, Table 3). The ingestion of 60 m.mole KCl was also followed by an increased potassium excretion, and there was a further rise in the excretion of this ion on overbreathing, to rates in excess of the normal filtered load (Fig. 3, Table 3).

The results of the renal clearance studies are summarized in Table 4, which gives data for two periods from each experiment, one control and one during hyperventilation. Each experiment contained seven periods, two control, two

in hyperventilation and three during recovery. The C_{IN} usually decreased by 5–10% during hyperventilation, and the plasma potassium fell by 0·4–0·7 m.equiv/l. The excretion of potassium always increased greatly during alkalosis and was made to exceed the filtered load, the clearance ratio C_K/C_{IN}

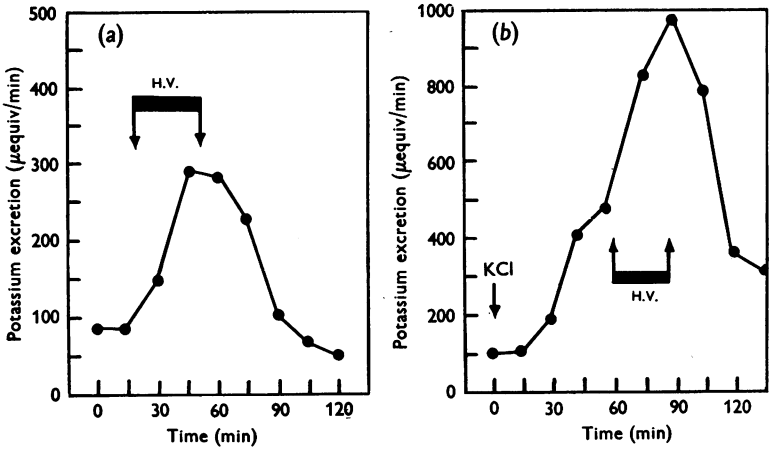

Fig. 3. Hyperventilation alkalosis and the renal excretion of potassium in man. The rate of excretion of potassium in μequiv/min plotted against time. Periods of hyperventilation marked ⇂⇂. (*a*) No potassium load. Subject S. Exp. 1. (*b*) 60 m.mole KCl was taken by mouth at ↓ KCl. Subject S. Exp. 4.

TABLE 3. The renal excretion of potassium in man before and during a 30 min period of hyperventilation. (*a*) No potassium load. (*b*) 60 m.mole KCl taken by mouth 1 hr before each experiment

	Potassium excretion (μequiv/min)		Urine pH	
Expt.	Before alkalosis	During alkalosis	Before alkalosis	During alkalosis
(*a*) S1	92	280	5·8	7·9
N1	291	631	6·5	8·0
F1	100	527	6·1	7·9
(*b*) S4	480	944	7·0	7·8
F4	330	654	7·1	7·5
N2	470	833	7·2	7·5

rising to 1·24. At the same time sodium excretion usually increased two to four times, despite a fall in the filtered load. The plasma bicarbonate was reduced from 25 to 15 m.equiv/l. and as the filtration rate also fell, the filtered load decreased by some 50%. Concurrently, bicarbonate excretion increased and the ratio C_{HCO_3}/C_{IN} rose from less than 0·001 to 0·20. Chloride excretion increased during hyperventilation alkalosis, although the filtered load was less.

TABLE 4. Acute respiratory alkalosis in man; the blood pH and the renal excretion of potassium and other electrolytes. Periods of 15 min, control (C) and hyperventilation (H.V.), paired from four experiments each containing seven periods, two control, two in hyperventilation and three during recovery. Expts. S, 5 and 6, no potassium load; Expts. S, 7 and 8, 60 m.mole KCl taken by mouth 1 hr before

Expt.		Blood pH	Plasma (m.equiv/l.) Na	K	HCO_3	Cl	C_{IN} (ml./min)	C_K/C_{IN}	K load (μequiv/min) $C_{IN} \times K_P$	Excretion rate (μequiv/min) K	Na	HCO_3	Cl
S5	C	7·36	140	4·8	25	103	118	0·14	566	87	284	0	263
	H.V.	7·50	142	4·1	19	102	108	0·60	443	266	271	114	288
S6	C	7·32	137	5·1	26	101	117	0·49	598	291	121	0	413
	H.V.	7·56	140	4·8	15	102	100	1·08	480	518	300	171	515
S7	C	7·44	142	4·6	26	102	115	0·50	529	266	525	180	562
	H.V.	7·58	142	4·4	17	102	108	1·04	475	496	564	346	611
S8	C	7·35	140	4·8	25	103	124	0·46	603	274	96	8	396
	H.V.	7·54	141	4·2	17	102	122	1·24	512	636	468	145	895

DISCUSSION

McCance & Widdowson (1937) first reported a potassium clearance greater than that of inulin in a patient suffering from pyloric stenosis, alkalosis and dehydration. More recently, Burnett *et al.* (1950) have also found increased rates of potassium excretion and high potassium clearances in a group of similar patients. The effect of alkalosis on potassium excretion is difficult to assess in pyloric stenosis as this condition is complicated by other factors which affect the excretion of this ion, such as starvation (Benedict, 1915), dehydration (Mudge, Foulkes & Gilman, 1950) and a low filtration rate (McCance & Widdowson, 1937). In the present experiments the changes in body pH and in potassium excretion were not the only variables, but as these differed in the three types of alkalosis it has been possible to reach a more general conclusion than could be derived from observations on a single kind of disorder.

The renal excretion of potassium consistently increased during alkalosis, whether this was produced by hyperventilation, chloride depletion or the infusion of sodium bicarbonate solutions. This increment in potassium excretion must be related either to changes in the glomerular filtrate or to alterations in tubular activity.

The changes in the load of electrolytes filtered at the glomerulus during acute alkalosis are summarized below:

	HCO_3	Cl	Na	K
Respiratory alkalosis	↓ ↓	↓	↓	↓
Chloride depletion alkalosis	↓ ↑	↓ ↓	↓	↓ ↓
Sodium bicarbonate alkalosis	↑ ↑	↓ ↑	↑	↓

There was a different pattern of change in the three types of alkalosis, the only common feature being a decrease in the filtered load of potassium. Despite this, potassium excretion was always enhanced during alkalosis.

Therefore there must be an alteration in the tubular transport of potassium in alkalosis which is independent of changes in the volume, and electrolyte composition, of the fluid delivered to the proximal tube.

The clearance ratio C_K/C_{IN} increased from normal values of 0·10–0·30 to well over 1·0 in all three kinds of alkalosis (Tables 1 and 4), which is interpreted as evidence for the secretion of potassium by the renal tubules. As the increment in potassium excretion was always associated with a fall in the filtered load of this ion, it is also possible that the tubular reabsorption of potassium was inhibited during alkalosis. The relative contribution to the rise in potassium excretion of an inhibition of reabsorption and a stimulation of secretion cannot be assessed. It will be shown later that both processes may have a common mechanism.

The renal secretion of potassium has previously been demonstrated during the intravenous infusion of potassium salts (Berliner, Kennedy & Hilton, 1950), in dehydration and in an osmotic diuresis (Mudge, Foulkes & Gilman, 1948). In the present dog experiments no extra potassium salts were given, and the ratio of the minute urine volume to the filtration rate (UV/C_{IN}) did not exceed 0·1, the level at which an osmotic diuresis begins to provoke an increase in potassium excretion. The dogs were well hydrated and there was an increase in cell water, a condition associated with the excretion of minimal amounts of potassium (Mudge *et al.* 1950) when there is no disturbance in acid-base balance.

This increased excretion of potassium may be considered as a primary response of the renal tubules to an alkalosis, or as secondary to changes in tubular activity with respect to other ions.

The excretion and reabsorption of Na^+, HCO_3^- *and* Cl^-. During the infusion of sodium bicarbonate the dogs were in a positive sodium balance, and the filtered load of this ion was increased. Under these conditions part of the increment in potassium excretion may be attributed to an exchange of Na^+ for K^+ in the cells of the renal tubules, a mechanism which has been described by Berliner *et al.* (1950). Indeed, a normal sodium balance may be essential for a high rate of potassium excretion during alkalosis. McCance & Widdowson (1936) found that when a respiratory alkalosis was induced in salt-depleted subjects the urine did not become alkaline and there was no increase in the excretion of sodium or potassium.

In the alkalosis of chloride depletion and in hyperventilation, the filtered load of sodium was decreased, yet the excretion of this ion rose. In this instance the secretion of K^+ cannot be explained as an exchange for Na^+, but may result from an exchange of K^+ with H^+ derived from carbonic acid:

$$\begin{array}{l} CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \\ \quad\quad\quad\quad\quad\quad \longleftarrow\!\!\!\!\text{———}\!\!\!\!\lrcorner \\ \quad\quad\quad\quad K^+ \longrightarrow K^+ + HCO_3^- \end{array}$$

This may also be considered as a tubular secretion of potassium and bicarbonate, without cation exchange. In either case the result would be an equivalent increment in excretion for both K^+ and HCO_3^-. In contrast, an increase in potassium excretion effected entirely by an exchange of K^+ for Na^+ does not require the renal tubular excretion of bicarbonate.

The observed increment in HCO_3^- excretion was usually much greater than that for K^+, and was associated with large increments in the excretion of both K^+ and Na^+. This may represent an exchange of H^+ for both Na^+ and K^+. There was a proportionate decrease in the reabsorption of bicarbonate as alkalosis developed, the ratio C_{HCO_3}/C_{IN} consistently rising from 0 to 0·30. The

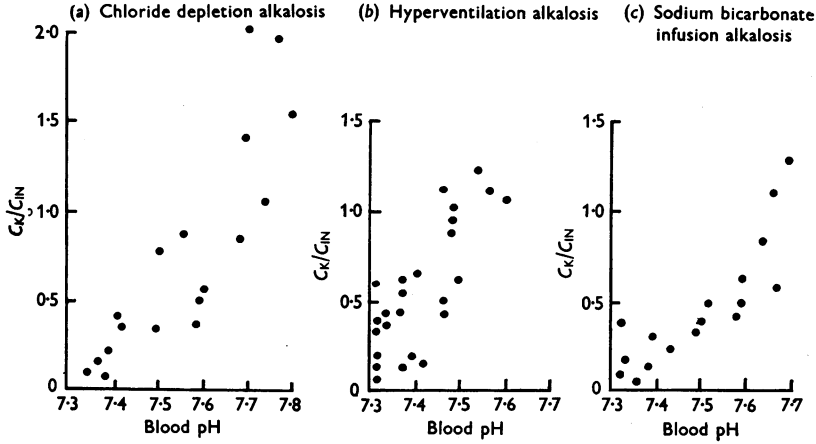

Fig. 4. Alkalosis and the renal tubular transport of potassium. The blood pH plotted against the clearance ratio C_K/C_{IN}. (*a*) Data from acute chloride depletion alkalosis experiments in the dog. (*b*) Data from acute hyperventilation alkalosis experiments in man. (*c*) Data from acute sodium bicarbonate infusion experiments in the dog.

filtered load of bicarbonate exceeds the tubular capacity for H^+ secretion during alkalosis, inhibition of carbonic anhydrase occurring as the pH rises (Roughton, 1935). The primary renal response to alkalosis may then be an increased excretion of bicarbonate, to which the increments in excretion of sodium and potassium are secondary. Whereas the excretion of bicarbonate, sodium and potassium ions always increased during alkalosis, the excretion of chloride ion cannot be related directly to changes in the body pH, and it merely conforms to the necessity of electroneutrality in the tubular fluid.

The change in tubular activity with regard to potassium shows a positive correlation with the blood pH (Fig. 4). The acid-base balance of the body is therefore one of the important factors which control the renal excretion of potassium. The renal mechanisms which control the excretion of individual electrolytes during alkalosis are closely interrelated. They cannot be described

in terms of fixed thresholds or by absolute reabsorption maxima, as required by systems which imply an excretion of ions related functionally only to the filtration rate.

SUMMARY

1. Renal clearance studies were made during acute experimental alkalosis in dogs and in man. The alkalosis was produced by three different methods: the removal of chloride by differential peritoneal dialysis; the intravenous infusion of sodium bicarbonate solutions, and by hyperventilation.

2. Potassium excretion increased in all types of alkalosis despite a negative balance for this ion. As the excretion of potassium exceeded the load filtered at the glomerulus there was evidence for the renal tubular secretion of potassium during alkalosis.

3. The renal excretion of potassium and bicarbonate ions during alkalosis is largely controlled by alterations in tubular activity, correlated with changes in the blood pH and with the availability of potassium for tubular secretion.

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